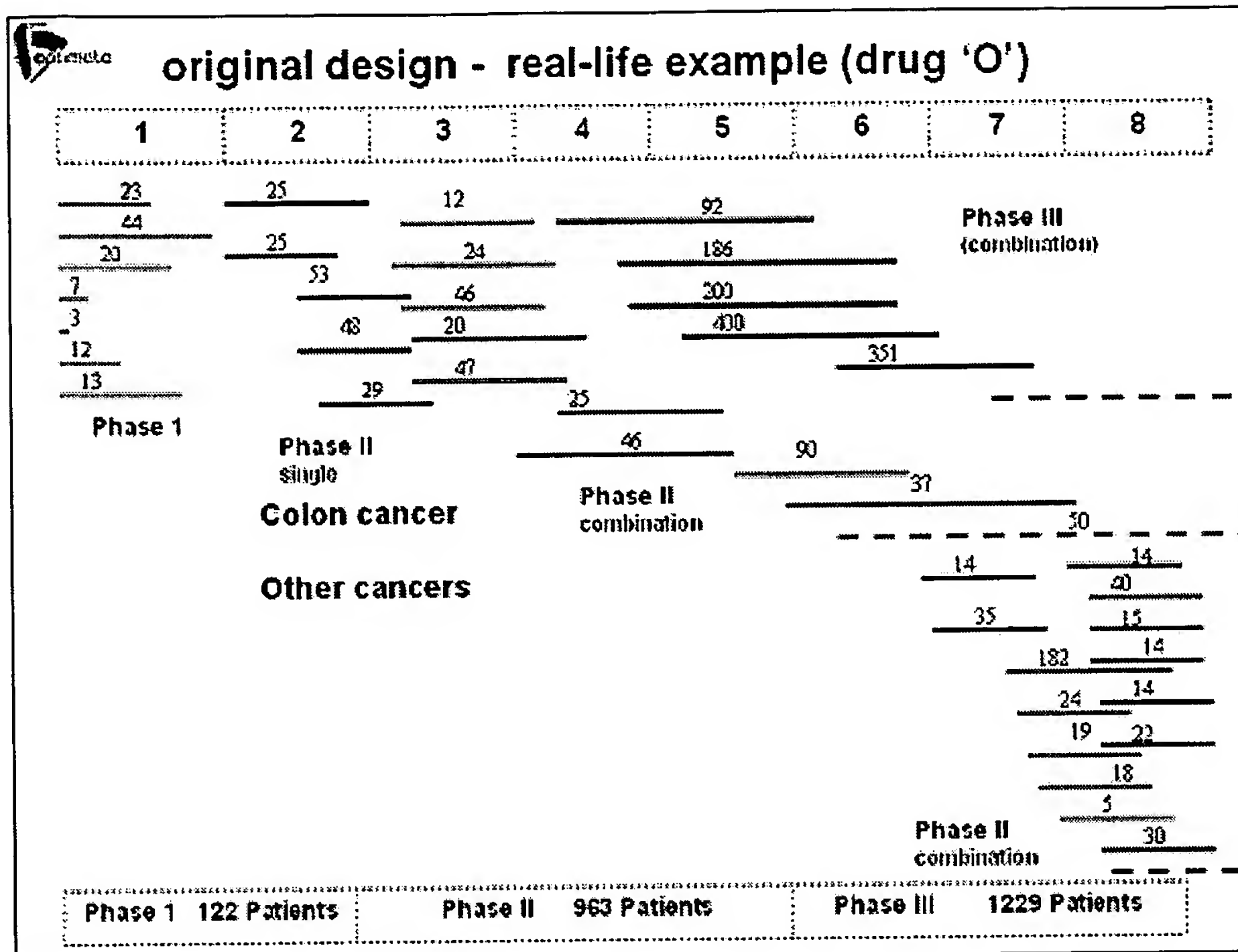
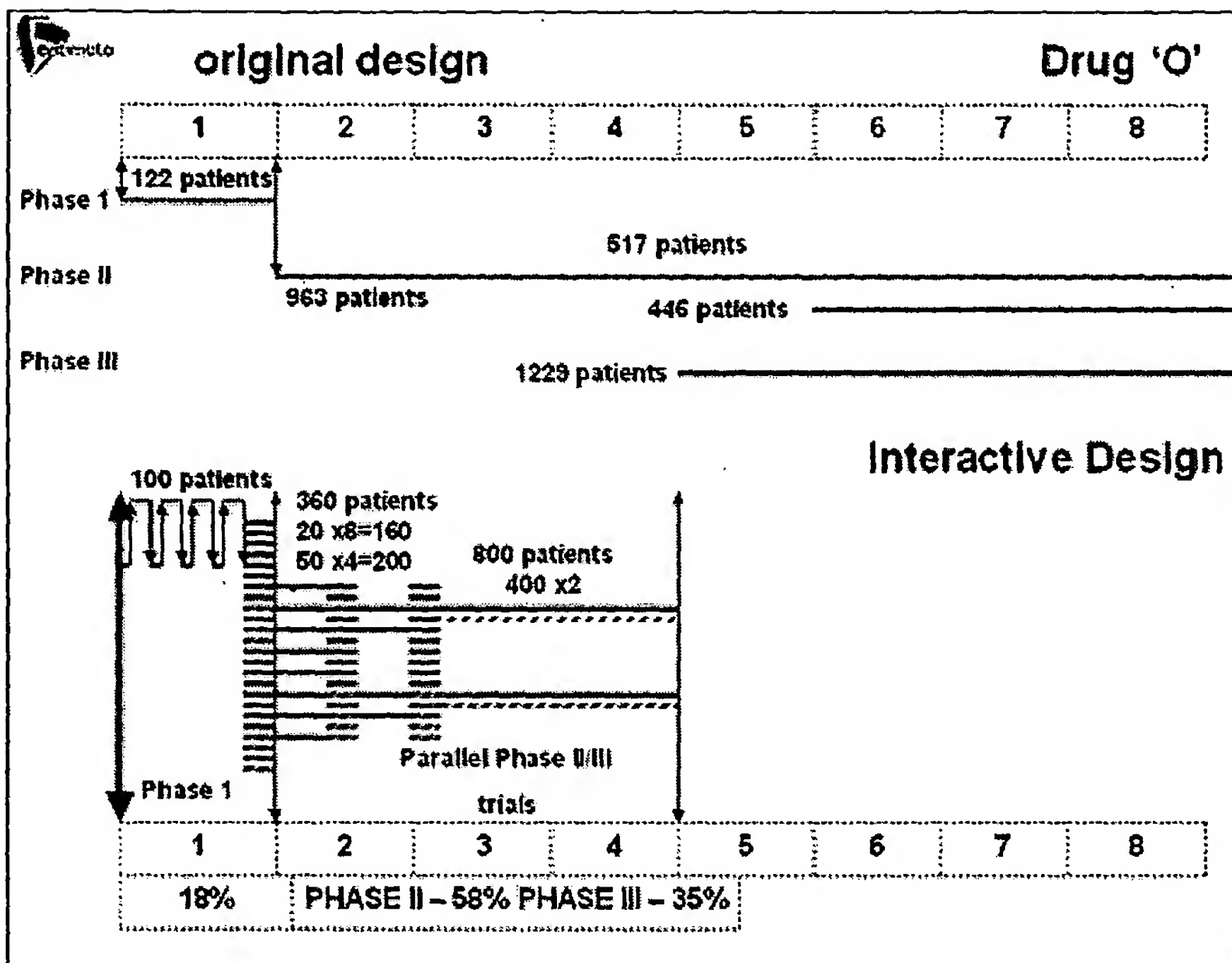


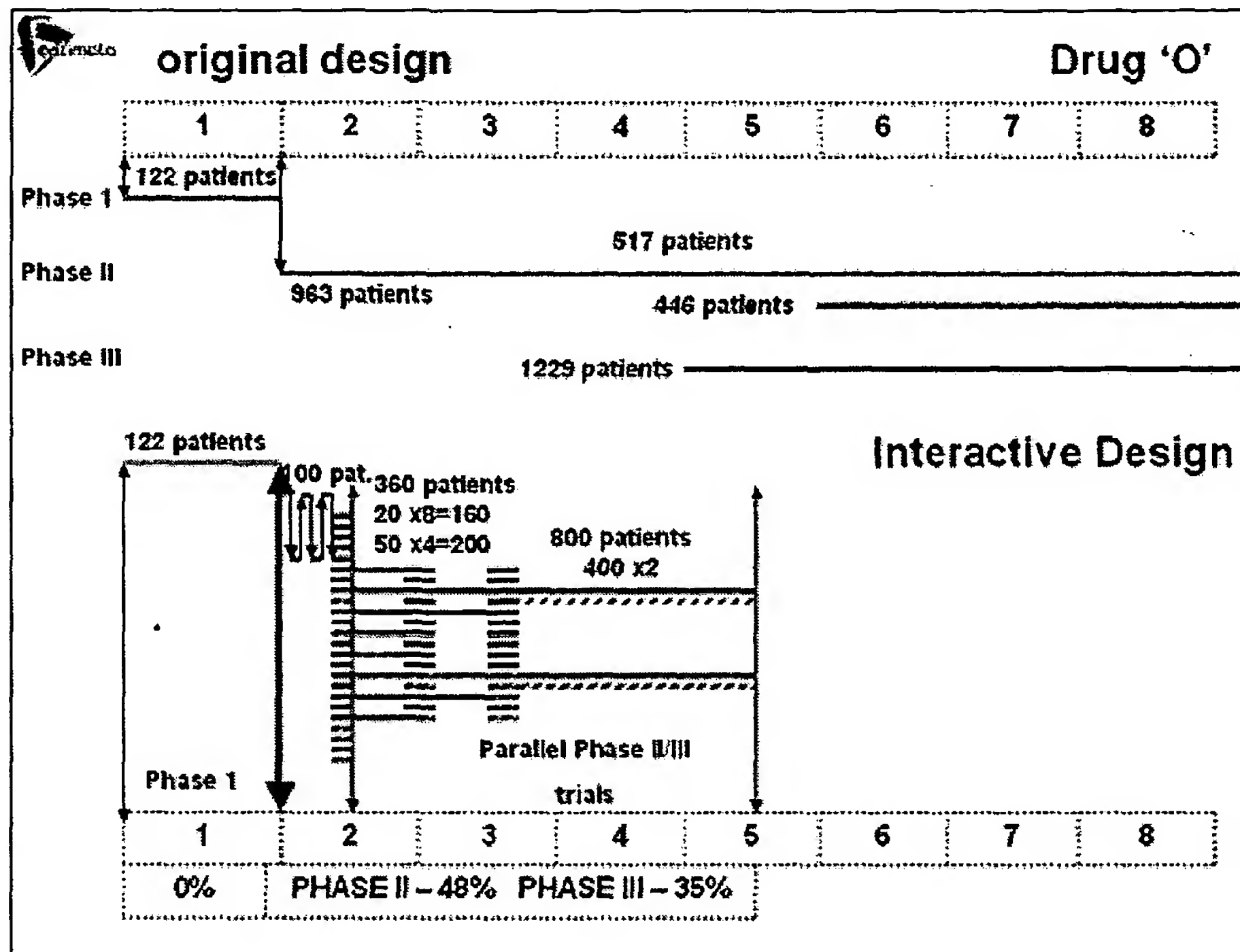
**Fig. 1.**



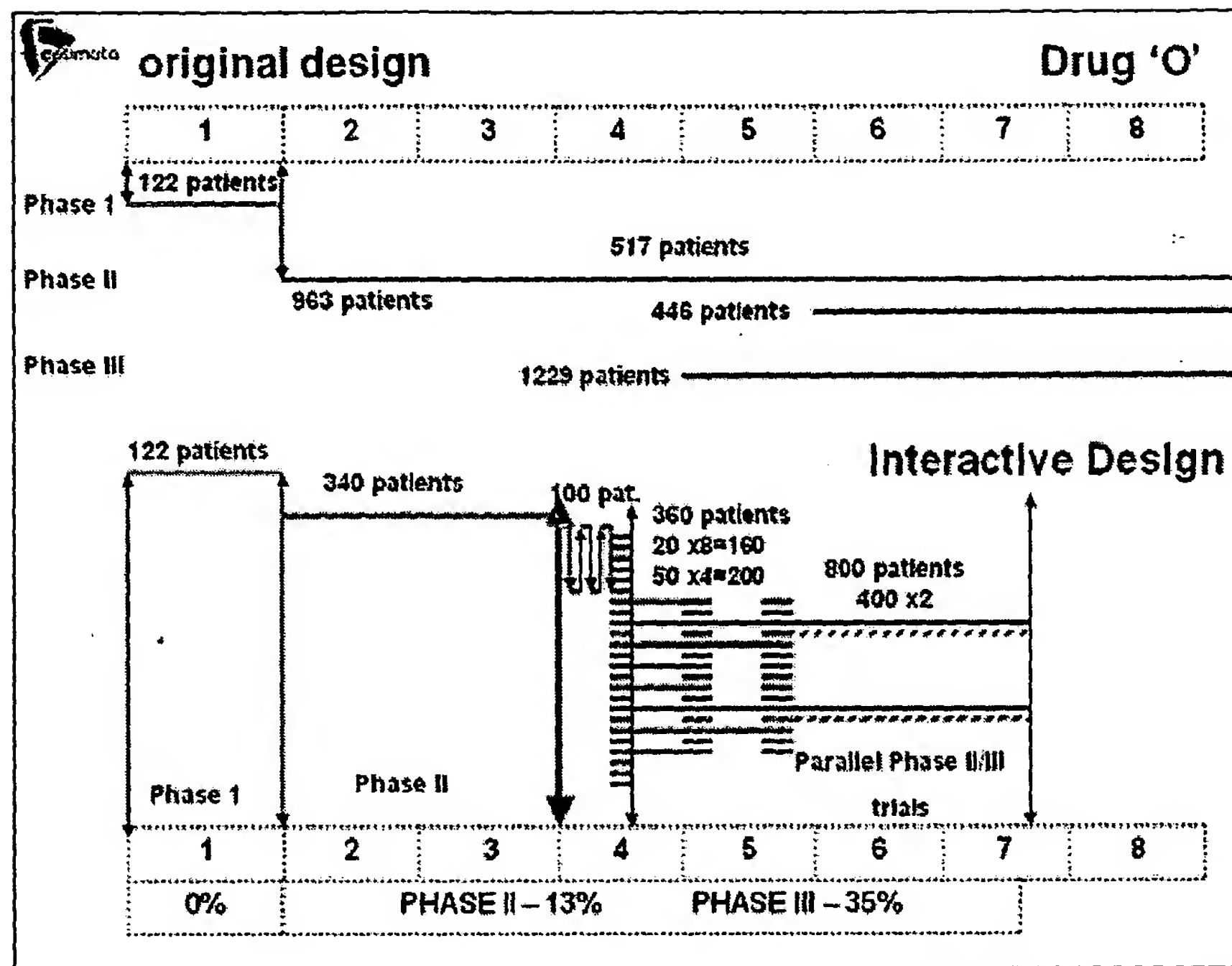
**Fig.2A.**



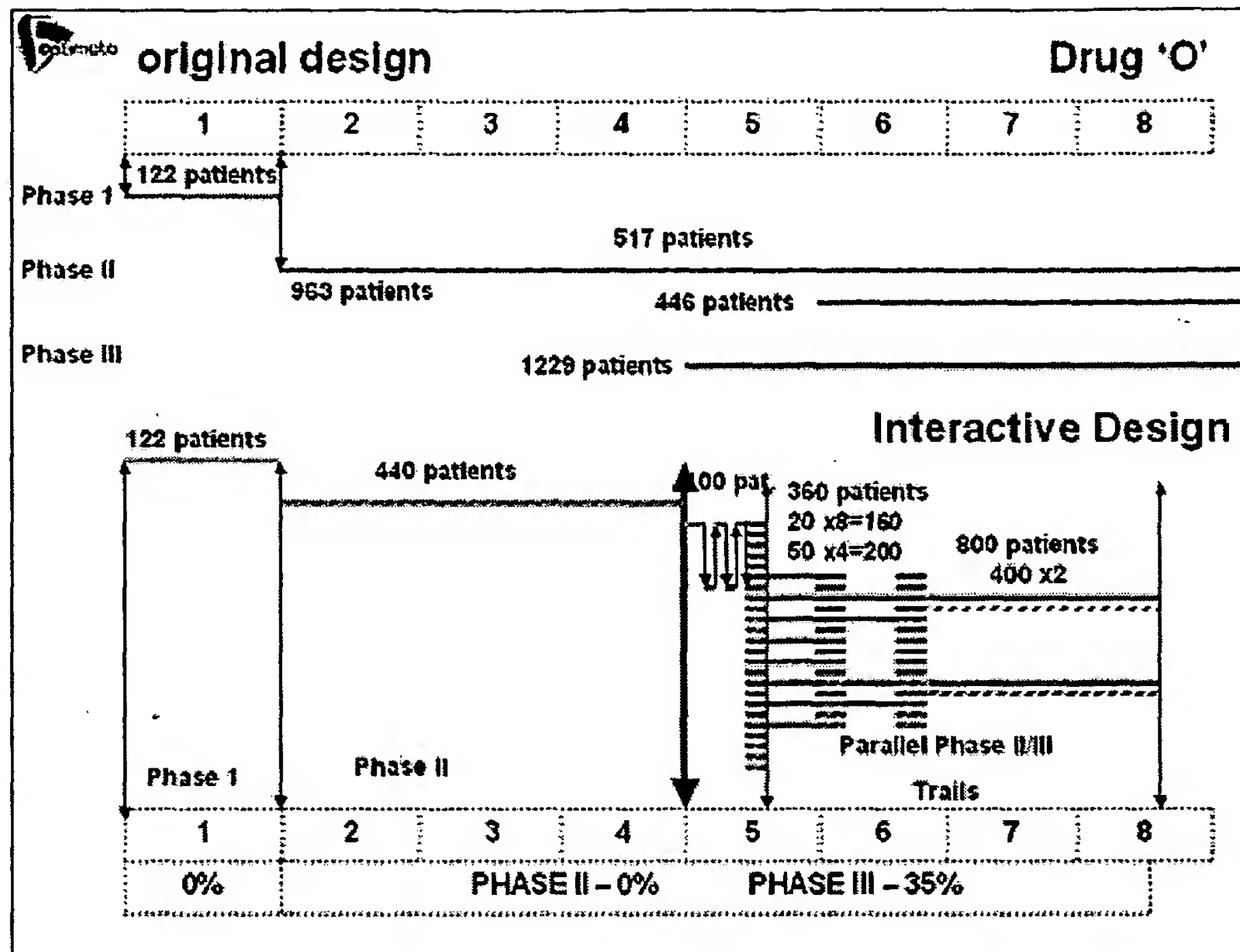
**Fig. 2B.**



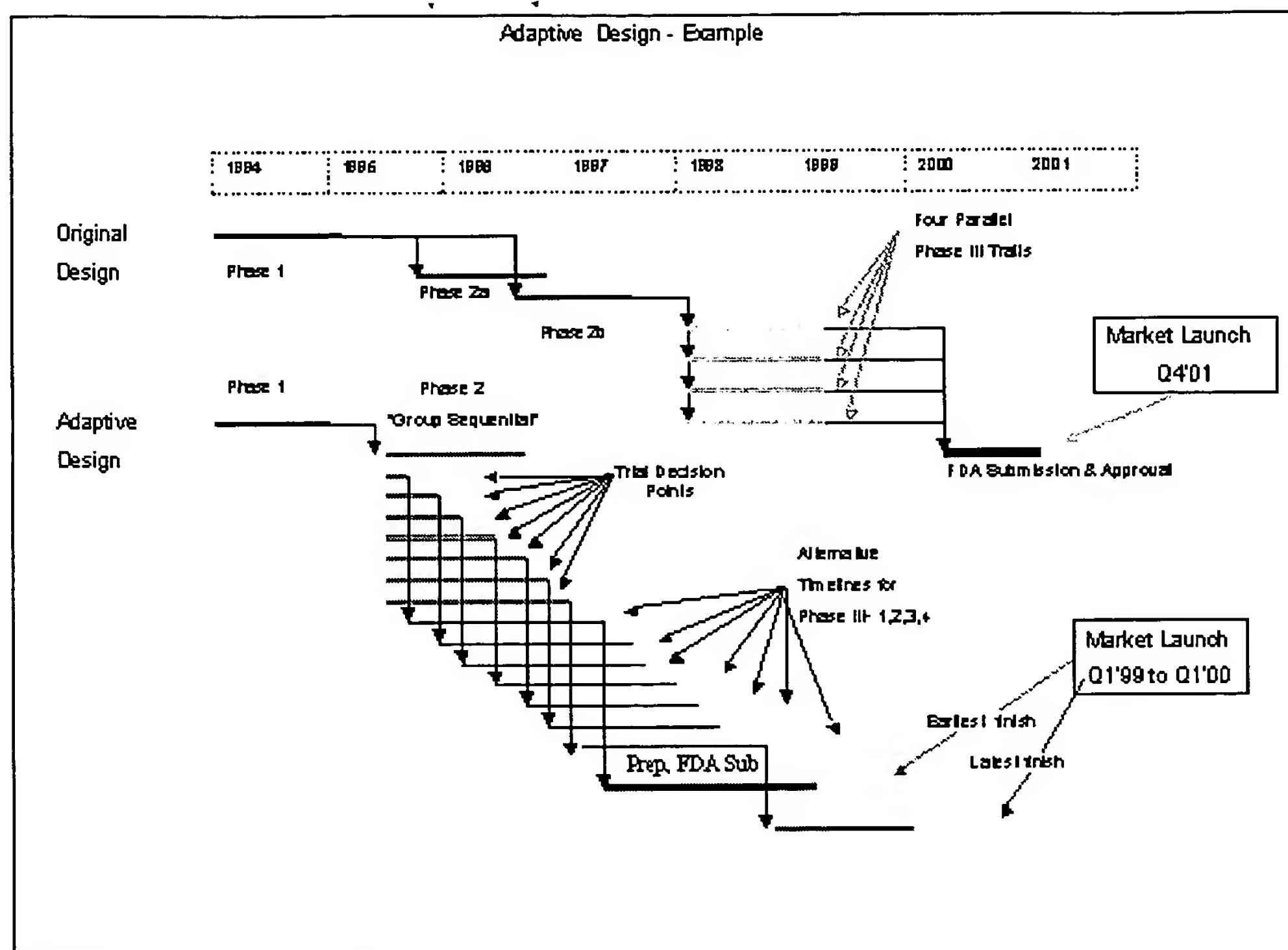
**Fig. 2C.**



**Fig. 2D.**



**Fig. 2E.**



**Fig. 3.**





# Preclinical Research

**In vitro**  $C_1=0$   $c=c_1$   $MA=A_1$   
 $MB=A_2$   $x=x_1$   $K_1=K_2=0$

Save  $C_1 = C_1 + c$

In rodent cells Save  $E_{C_1}(r_{tc})$

In human cells Save  $E_{C_1}(h_{tc})$

no  
 $E_{C_1} - E_{C_1-c} > X$   
 yes

no  
 $E_{C_1} - E_{C_1-c} > X$   
 yes

$K_1 = K_1 + 1$

$K_1 = 0$

$K_2 = K_2 + 1$

$K_2 = 0$

no  
 $K_1 = MA$   
 yes

**Transfer  $E_{C_1}$  to IC**  
 In rodent  $EC_1(r_{tc}) \dots IC_{100}(r_{tc})$   
 In human  $EC_1(h_{tc}) \dots IC_{100}(h_{tc})$

yes  
 $K_2 = MB$   
 no

Fig. 5A

# Preclinical Research

**In vivo rodent**  $D_1=0$   $d=d_1$   $M_1=A_1$   
**population**  $M_2=A_2$   $K_1=K_2=0$

Save  $D_i = D_1 + d$

Save Concentration in blood  $C_{Di(BL)}(r)$   
 in target tissue j  $C_{Dij(TT)}(r)$   
 Efficacy in target tissue j  $E_{Dij(TT)}(r)$

cause of death

Save Concentration  
 in toxicity tissue k  $C_{Dik}(r_{Tox})$

In vitro Save  
 $E_{CDi}(r/h_{Tox})$

Drug  
 induced  
 death

Save side effects

$P=0$

$P = \% \text{ of death}$

Save  $LD_p(r)$

$\% \text{ of death}$   
 $>90$

$D_i = LD_{10}(r)$

Fig. 5 B

# Preclinical Research

## In vivo non rodent testing

$$d=d_2$$

Save Concentration in blood  $C_{Di(BL)}(nr)$ ;  
in target tissue  $j$   $C_{Dij(TT)}(nr)$ ;  
in toxicity tissue  $k$   $C_{Dik(Tox)}(nr)$ ;

Drug  
induced  
death

$$\text{Save } LD(nr)=D_i$$

$$D_i = D_i - d$$

no

yes

$$LD_{10}(r)=LD(nr)$$

$$D_0(PI) = LD(nr)/6$$

$$D_0(PI) = LD_{10}(r)/10$$

End of preclinical  
research

Fig. 5c

# Preclinical Research

in vivo (in time)										in vitro (in time)			
	$C_{Di(BL)}(t)$	$C_{Dij(TT)}(t)$	$C_{Dik(Tox)}(t)$	$E_{Dij(TT)}(t)$	$LD_P(t)$	$C_{Di(BL)}(nr)$	$C_{Dij(TT)}(nr)$	$C_{Dik(Tox)}(nr)$	$LD(nr)$	$E_{cij}(r_{ic})$ $EC(r_{ic})$	$E_{cij}(h_{ic})$ $EC(h_{ic})$	$E_{cdik}(r_{tox})$ $EC(r_{tox})$	$E_{cdik}(h_{tox})$ $EC(h_{tox})$
$D_i$													
$D_0$	■	■	■	■	■	■	■	■	■	■	■	■	■
.													
$D_{T_0}$	■	■	■	■	■	■	■	■	■	■	■	■	■

Develop Computer PK/PD Model

End of preclinical research



## Clinical Trial Phase I

Fig. 5D



$D_1 = D_0(\text{PhI})$   $d=d_2$   $X=X_2$   $F_1=0$   $F_2=0$   $F_3=0$   
 $M_1=B_1$   $M_2=B_2$   $M_3=B_3$   $n_1=s_1$   $n_2=s_2$   $Z_1=0$   $Z_2=0$   $Z_3=0$

# Clinical Trial Phase I

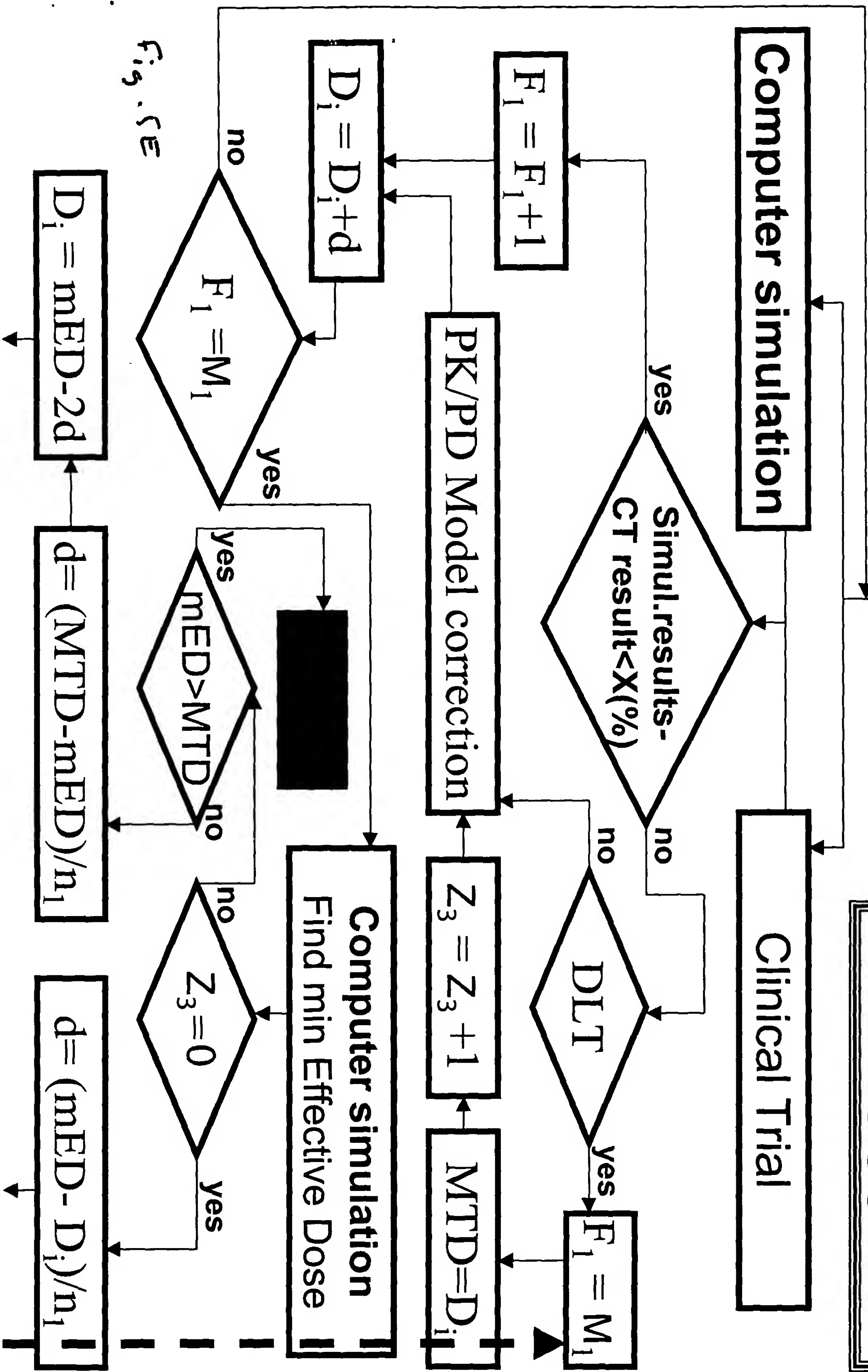


Fig. 5E

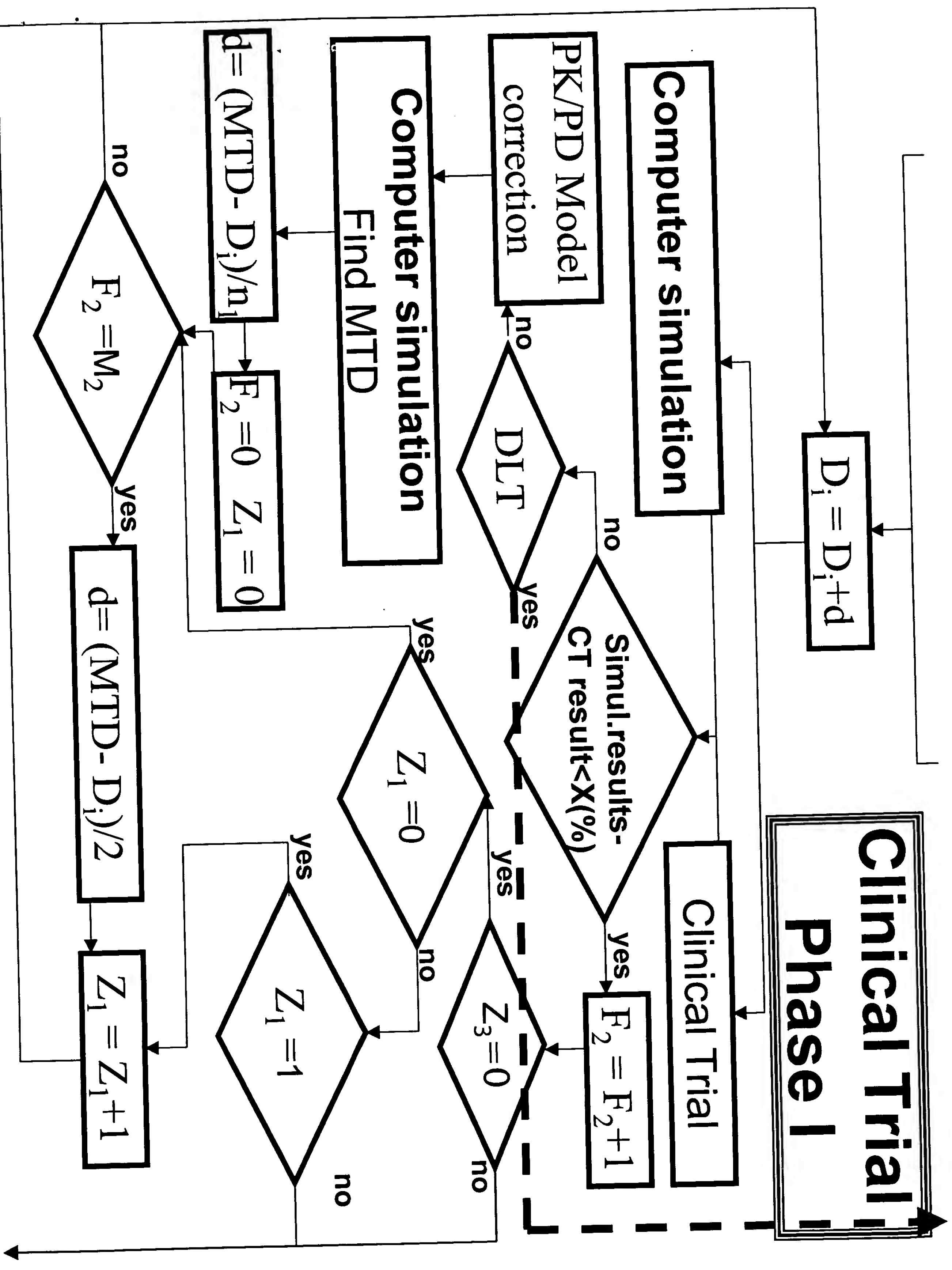


Fig. 5f

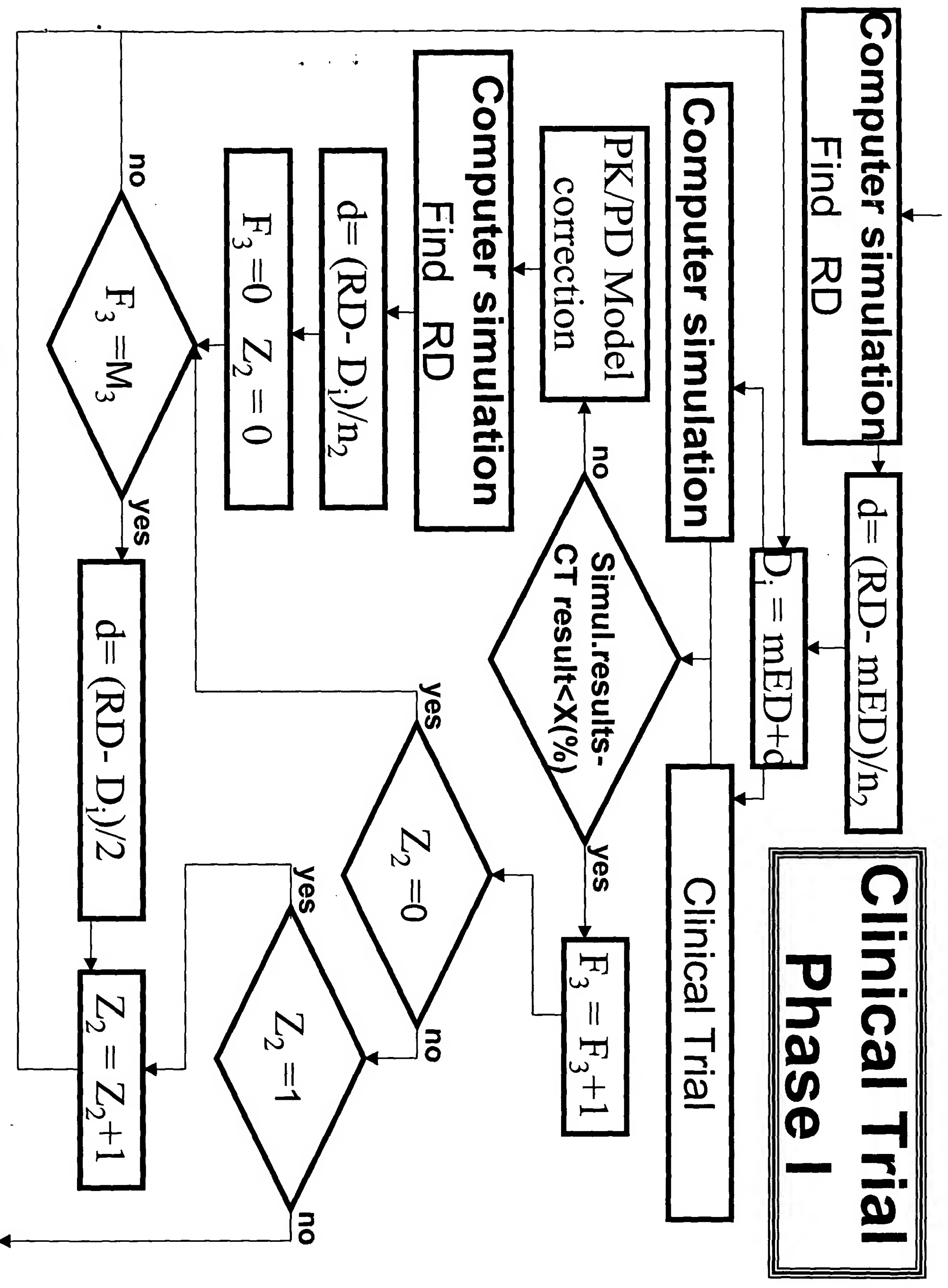


Fig 56

# Clinical Trial Phase I

**Computer simulation**  
Find Recommended Dose ( $D_i$ ) &  
Dosing Interval ( $T_i$ ) for checking  
Drug Cumulative effect

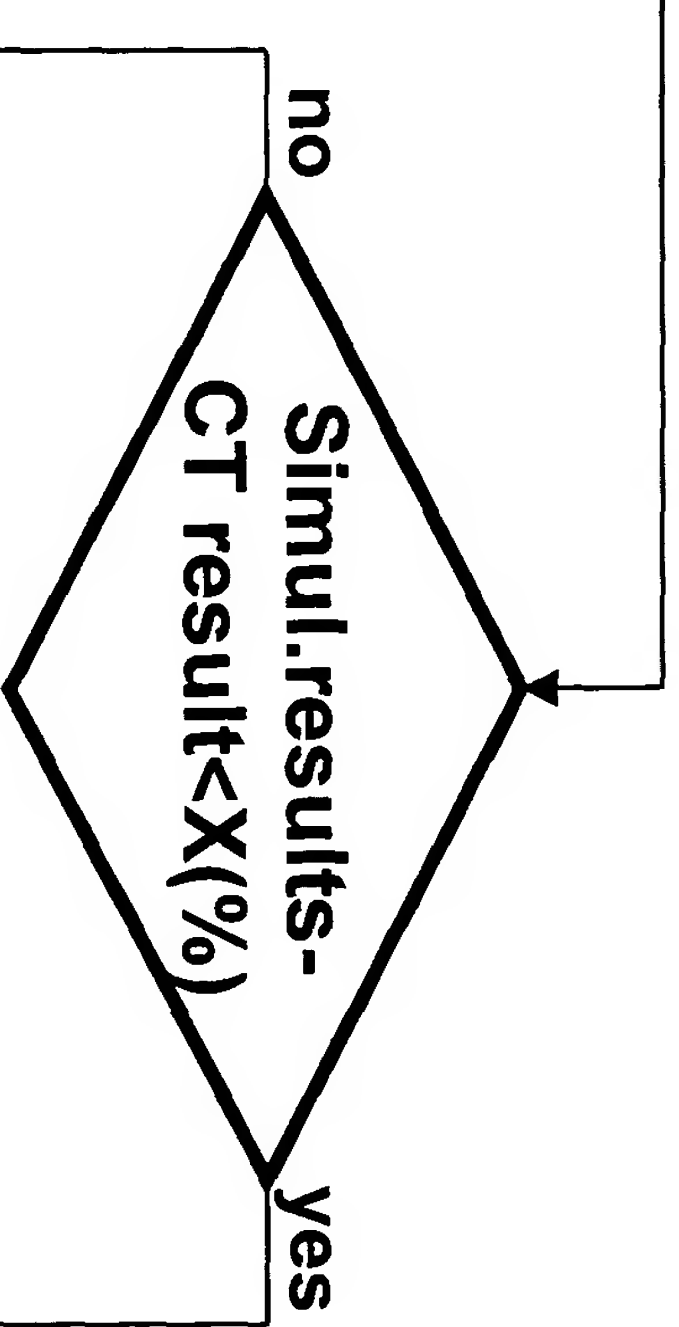
Clinical Trial  $D_1$  &  $T_1$

Clinical Trial  $D_2$  &  $T_2$

•  
•  
•

Clinical Trial  $D_{n-1}$  &  $T_{n-1}$

Clinical Trial  $D_n$  &  $T_n$



PK/PD Model  
correction

End of Clinical Trial Phase I research



## From Phase I

Find optimal monotherapy treatment protocols for cancer type  $w$  (also considering toxicity)

- Analysis of computer simulation results;
- "GO - NO GO" recommendations
- Which monotherapy and combinational treatment protocols would give the best clinical results?

## Computer simulation Between Phase I & Phase II

For cancer type  $w$  ( $w=1, n$ ) & patient population  $v$  ( $v=1, m$ )

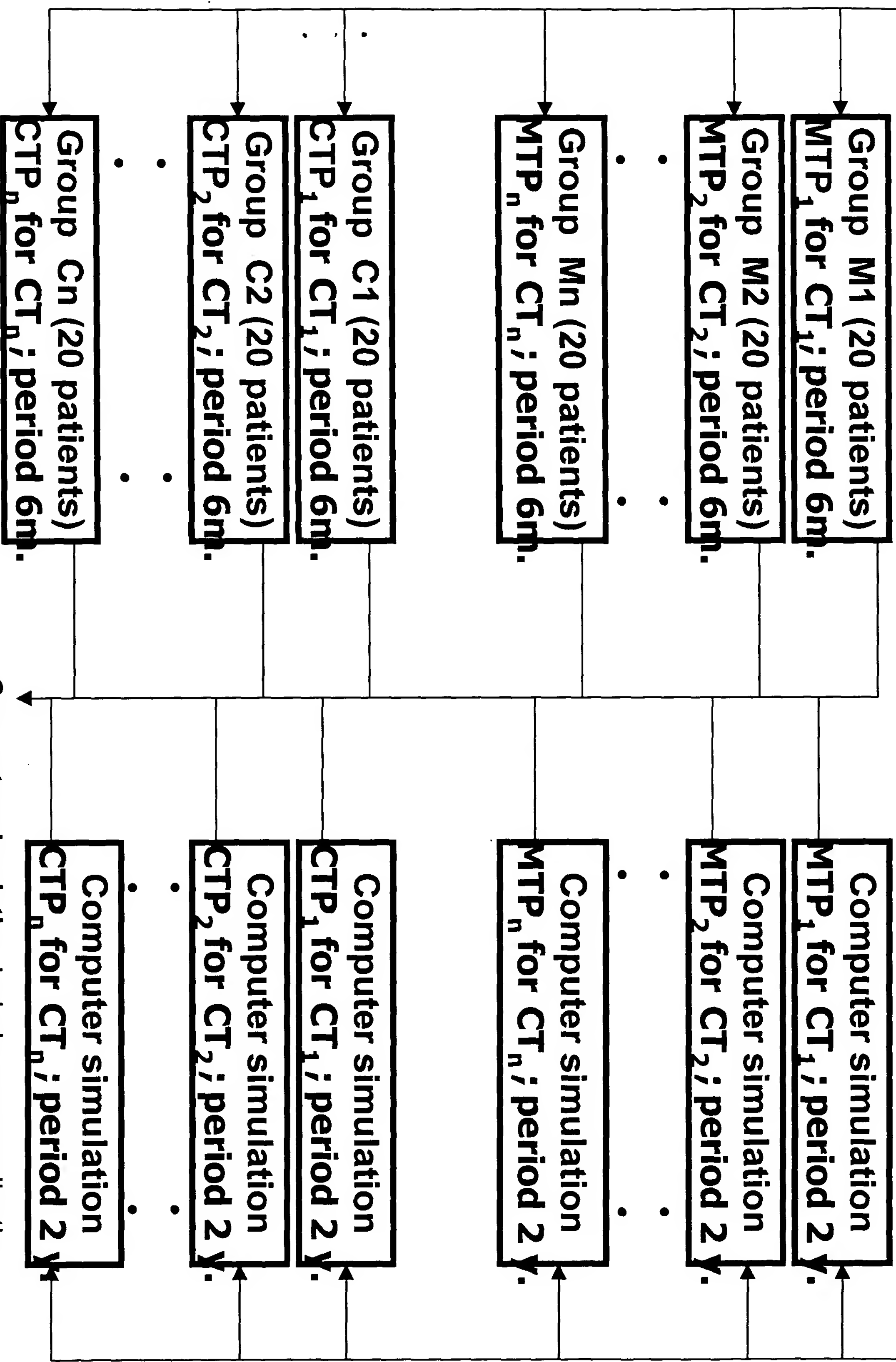
For patient population  $v$  find cancer growth parameters, influence on which, in addition to trial drug effect, would give the best clinical results

Find in drug database the drug(s) that has an effect on the desired cancer growth factors/is today's 1<sup>st</sup> line therapy

Find optimal combination treatment protocols for cancer type  $w$  (also considering toxicity)

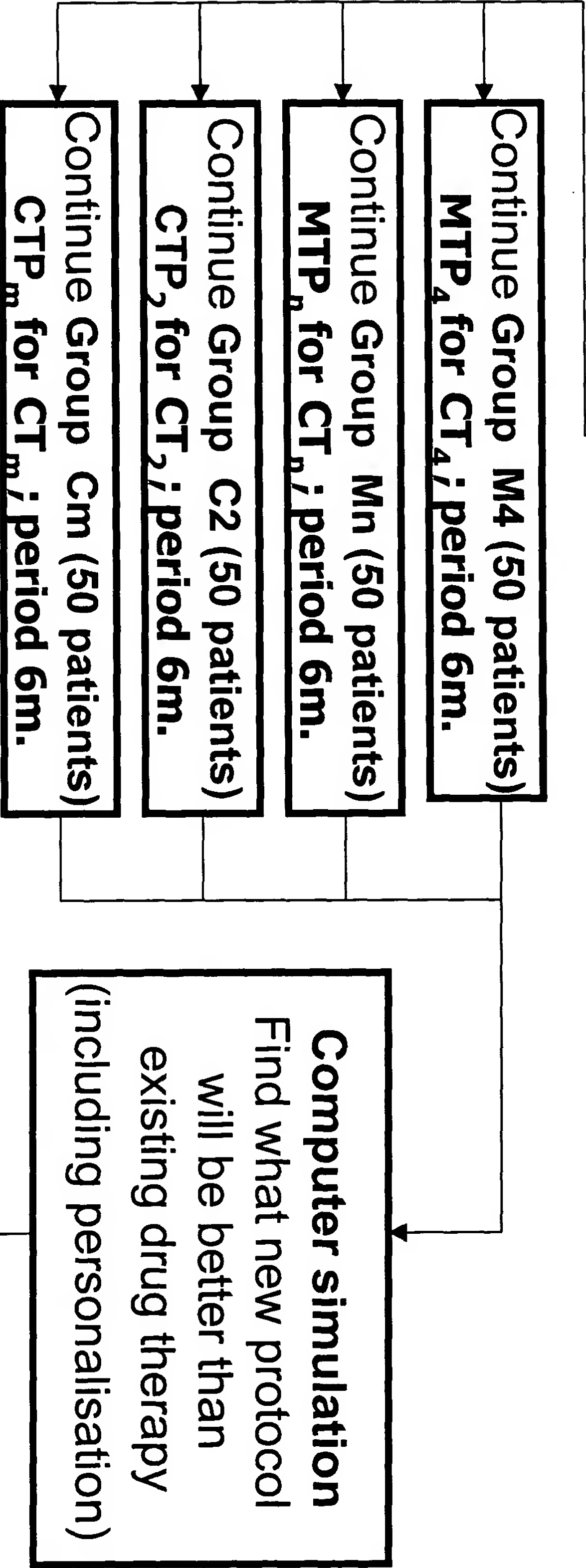
To Phase II

# Clinical Trial Phase II



# Clinical Trial Phase II

Analysis of 6 Months Clinical Trial  
Results and 2 years Computer Simulation  
Results for most promising mono- and  
combination treatment protocols.



End of Clinical Trial Phase II research

Fig. 5k

# Clinical Trial Phase III

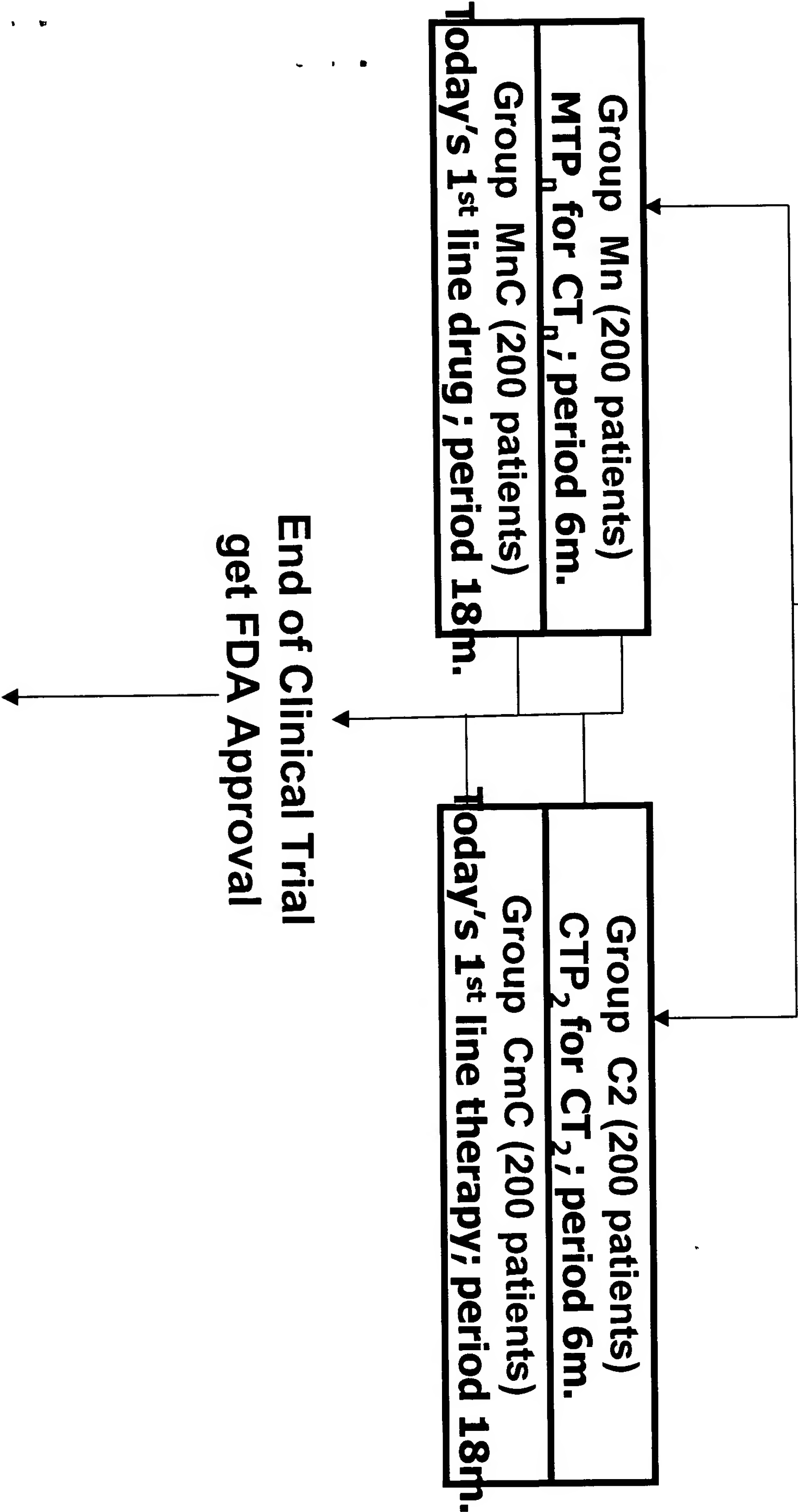
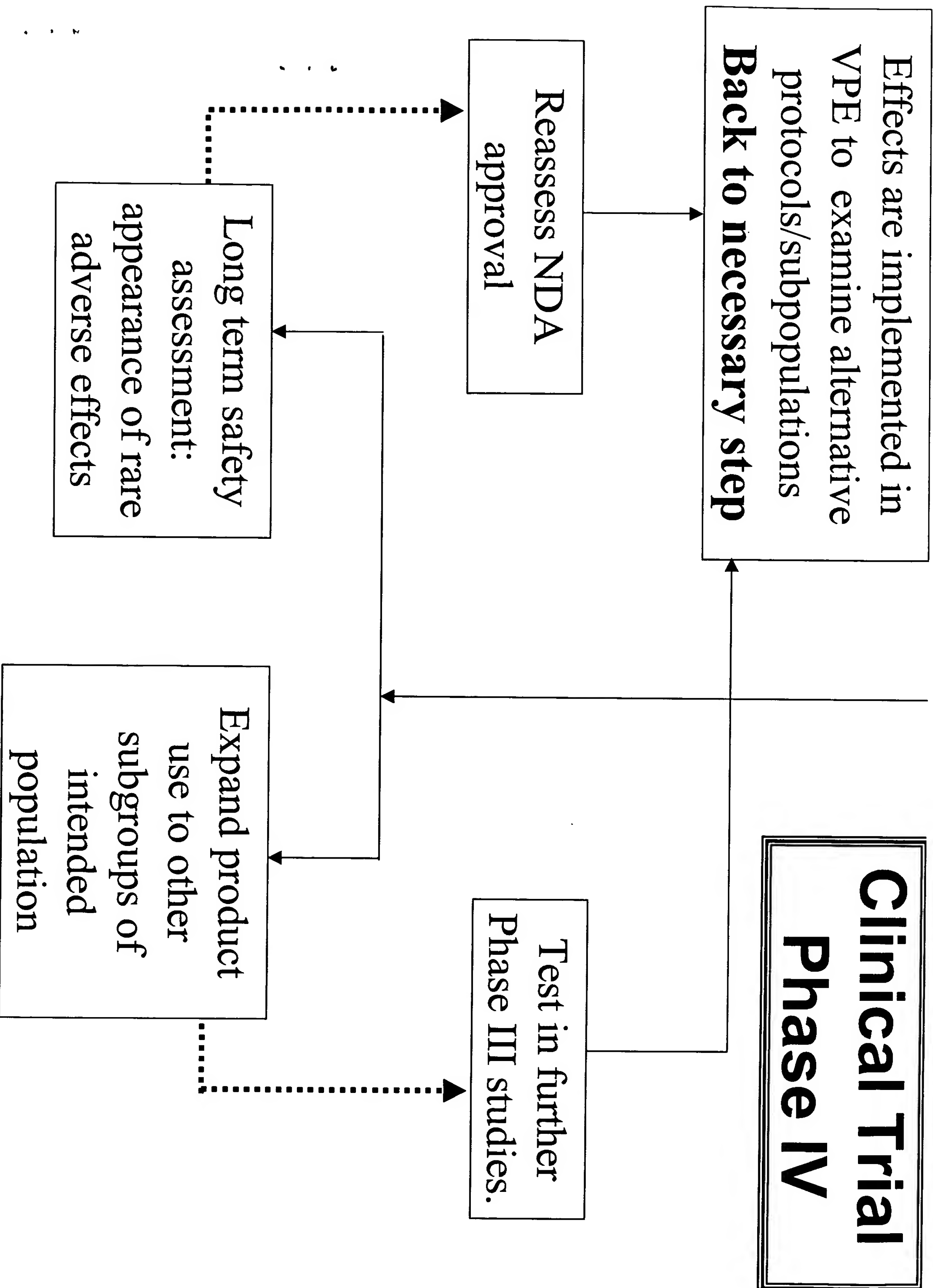


Fig. 52





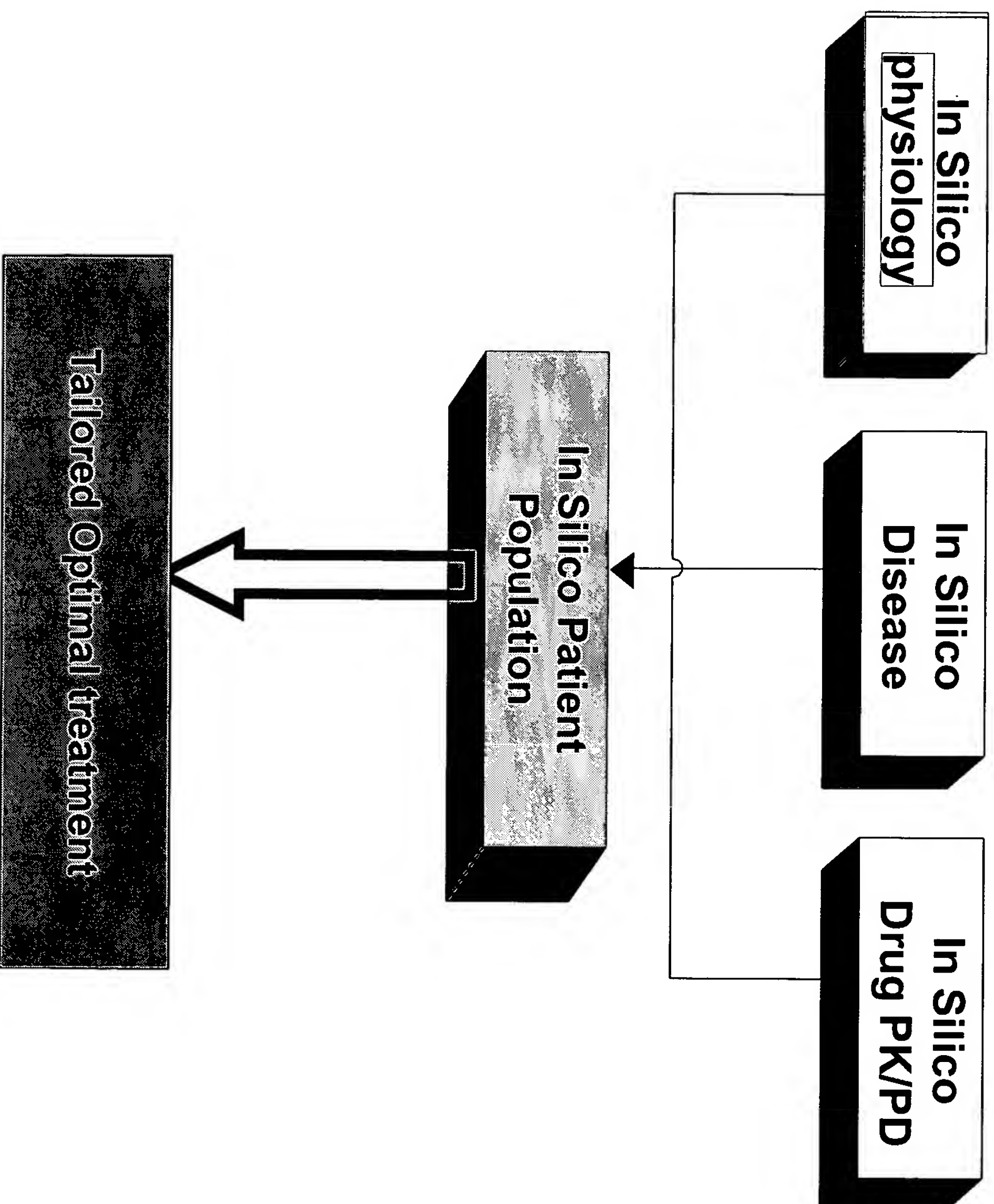


Fig. 6